REMARKS

Claim 15 has been amended to recite that the racemic mixture of a propionic acid derivative is provided with a hydrocolloid coating. This amendment has been made in view of the disclosure of WO 91/16043 ("Mapelli") concerning dissolution or swelling of the membrane coating in the oral cavity that liberates an unpleasant taste. Support for the amendment is found throughout the specification at, for example, page5, line 13 to e 6, line 2.

Claims 19-21 have been amended in view of the amended to claim 15, discussed above. In particular claim dependencies for claims 20 and 21 were amended and the hydrocolloid coating element of claim 12 was deleted.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

Obviousness-type Double Patenting

THE EXAMINER REPEATED A PROVISIONAL REJECTION BASED ON AN ABANDONED APPLICATION

Claims 1, 2, 4, 6, 9-13 and 15-22 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting. (August 23, 2005 Office Action ("Office Action") at 2). The Examiner alleged that claims 1, 2, 4, 6, 9-13 and 15-22 of the instant application "are unpatentable over claims 1-8 of co-pending Application No. 09/002,447 in view of Mapelli."

USSN 09/002,447 was abandoned on November 19, 1999. Because the application that formed the basis for the instant rejection is not co-pending, the rejection is improper and must be withdrawn.

Obviousness Rejections

1. **THE EXAMINER REPEATED THE REJECTION OF CANCELLED CLAIMS 1 AND 9**

Claims 1 and 9 were **again** rejected under 35 USC §103(a) as being unpatentable over U.S. Pat. No. 5,541,227 ("Loew") in view of PCT Appl. No. WO 91/16043 ("Mapelli") further in view of U.S. Pat. No. 5,780,046 ("Humber"). (August 23, 2005 Office Action ("Office Action") at 4).

For the reasons set forth below the rejection, respectfully is traversed.

Claims 1 and 9 were cancelled in the August 5, 2003 Preliminary Amendment. Accordingly, it is believed that this rejection is moot. This is the second request for withdrawal of the instant rejection. The rejection must be withdrawn.

2. **THE EXAMINER REPEATED THE REJECTION OF CANCELLED CLAIMS 1-14**

Claims 1-22 were **again** rejected under 35 USC § 103(a) as being unpatentable over Loew in view of Mapelli further in view of U.S. Pat. No. 4,835,187 ("Reuter") (Office Action at 5.)

For the reasons set forth below the rejection, respectfully is traversed.

Claims 1 -14 were cancelled in the August 5, 2003 Preliminary Amendment. Accordingly, it is believed that this rejection is moot. This is the second request for withdraw of the instant rejection. The rejection must be withdrawn.

In order to expedite prosecution on the merits and to place the instant application in condition for allowance, the following is provided as if the rejection were made to solely to claims 15-22.

Loew discloses

[57] **ABSTRACT**

An ibuprofen-containing medicament which contains ibuprofen only in the (S)-(+)-form is disclosed. (S)-(+)-ibuprofen is more than twice as active as the racemate which has until now been used in the treatment of rheumatism. This permits reduction of the quantity of active ingredient and the size of the tablets or dragees.

Ibuprofen, i.e. 2-(4-Isobutylphenyl)-propionic acid is a tried and tested NSAR from the group of phenyl propionic acid derivatives that has shown itself to be effective in inhibiting prostaglandin synthesis in experiments with animals with inflammation. In therapy of humans, ibuprofen reduces pain, swelling and fever caused by inflammation. It shows the usual unwanted side effects of NSAR. The pharmacological activity is accounted for by only one of the enantiomers. It is known that (R)-(−)-ibuprofen has substantially less pharmacological activity than (S)-(+)-ibuprofen. Since, however, the ineffective (R)-(−)-enantiomer is con- Col. 1

Col. 1

verted to the active (S)-(+)-enantiomer in vivo, as has been proved by analysis of ibuprofen metabolites excreted in the urine, no therapeutic advantage has until now been expected from the use of the (S)-(+)-form instead of the racemate and a separation of the dextro rotatory form from the laevo rotatory form has not been thought to be necessary.

It has now been found that, contrary to established opinion, according to which the ibuprofen-racemate was the most suitable therapeutically-active form since the inactive (R)-(−)-enantiomer was converted into the active (S)-(+)-enantiomer in humans, that the (S)-(+)-form of ibuprofen, i.e. in the absence of the (R)-(−)-form has a substantially greater pharmacological potential than was anticipated. The present invention is based on this recognition.

The invention relates to an ibuprofen-containing medicament and is characterized in that in the medicament ibuprofen is only present as the (S)-(+)-enantiomer. It was not to be expected that by the sole use of the (S)-(+)-enantiomer a substantial reduction of dosage would be possible, since it was known that the as such largely inactive (R)-(−)-ibuprofen was converted into the active (S)-(+)-ibuprofen in humans. It was, however, surprisingly found that the same analgetic activity caused by a given dose of racemic ibuprofen can not only be achieved by half the dose of (S)-(+)-ibuprofen, but that even less than half as much (S)-(+)-ibuprofen as racemic ibuprofen is required to give a given analgetic activity. This result is, on the basis of observations until now on the mechanism of action of NSAR, particularly ibuprofen, extremely surprising. These

Evaluation of the Analgetic Activity of Ibuprofen

In this test the afferent nerves of the feet of female Rhesus monkeys were electrically stimulated. For the test four adult female Rhesus monkeys (macaca mulatta) were used.

The following active ingredients were used:
(S)-(+)-ibuprofen
(R)-(−)-ibprofen
(±)-ibuprofen
Acetylsalicylic acid

Col. 6

Each animal was treated with the following active ingredients in the given quantities:

1. (S)-(+)-Ibuprofen	50 mg/kg
2. (R)-(−)-Ibuprofen	50 mg/kg
3. (±)-Ibuprofen	50 mg/kg
4. acetylsalicylic acid	100 mg/kg
5. carrier (0.5% carboxymethyl cellulose	

Col. 6

TABLE 1

Percentage change of the voltage required to achieve a stimulus response in the female Rhesus monkeys

Treatment	Oral Dose (mg/kg)	Median percentage change in the threshold voltage at various times (h) after administration of the effective ingredient							
		0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0
Carrier	—	−6.6	−4.8	−13.0	−7.4	−4.3	−5.6	−11.5	−6.9
(+)-S-Ibuprofen	50	+9.5	+33.5*	+51.2*	+53.9	+45.5	+42.3	+33.7	+38.2
(−)-R-Ibuprofen	50	−5.7	+4.0	+4.5	+0.5	−4.7	−7.0	−2.3	−3.4
(+)-Ibuprofen	50	+6.4	+8.4	+15.7	+15.7	+8.5	+18.1	+9.7	+17.0
Acetylsalicylic Acid	100	+35.8	+56.6*	+41.4	+80.4	+74.6	+72.8	+66.1	+59.8

Statistical analyses carried out using the Mann-Whitney U Test
*P < 0.05 compared to the carrier

Mapelli discloses taste masking of an orally administered drug by coating the drug with a polymeric membrane soluble only at a pH of 5 of greater. An acid substance is included in the formulation to reduce or prevent the dissolution of the membrane in the oral cavity.

Mapelli also discloses:

(57) Abstract

The taste of orally administered drugs is masked by coating the drug with a polymeric membrane which is soluble or pH of 5 or more. An acid substance is included in the formulation containing the coated drug to reduce or prevent the diss of the membrane in the oral cavity.

cavity.

It has now been found that this difficulty can be avoided or minimized by adding acidic substances to the orally administered pharmaceutical forms such that the acidic substances dissolve to create a microenvironment around the coated particles, which prevents the dissolution of the polymers making up the membrane. Thus the taste masking is maintained in the oral cavity by the coating on the drug.

Accordingly the present invention provides a pharmaceutical formulation for oral administration comprising

a core comprising a drug, said core being coated with a polymeric membrane which is soluble only at a pH of 5 or greater

and an acidic compound for reducing or preventing the dissolution of the membrane in the oral cavity.

Mapelli at 1.

Unfortunately however many drugs have an unpleasant, bitter or irritating taste and therefore it is necessary to mask the taste. In order to mask the taste, particles of the drug may be coated with a membrane which prevents the release of the drug in water (if taken with water before ingestion) and in the oropharyngeal cavity during ingestion but liberates the drug after ingestion.

The most suitable membranes for this purpose are impermeable to water and saliva but dissolve as a function of the gastrointestinal pH. Among the most common membranes are those constituted by polymers which are insoluble in water or in acid environments but are soluble at pH greater than 5 as found in the intestine. However the pH of saliva is also greater than this value and so the partial dissolution of the membrane with consequent release of the unpleasant taste of the drug can begin in the oropharyngeal

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Mapelli at 1.

The formulation may be prepared by coating the core with a polymer which forms the polymeric membrane and adding the acidic compound to the formulation.

The invention also provides a method for masking the taste of drugs contained in pharmaceutical formulations, in which the taste of the drug is masked by coating with a polymeric membrane which is soluble only at a pH of 5 or greater characterised in that an acidic compound is added to the formulation in order to reduce or prevent the dissolution of the membrane in the environment of the oral cavity.

Mapelli at 2.

According to the invention the drug will be released only when the coated cores (ie particles) have passed through the stomach and reached the intestine where there is a pH equal to or greater than 5 (this occurs rapidly especially if the stomach is empty, and when dealing with particles of small dimensions).

Another proposal suggests that a taste masking action may be obtained with a membrane which is insoluble at a high pH (greater than 5) and soluble at a low pH (1.2 - 1.5) such as for example Eudragit E; this would be insoluble in the oral cavity (thus having a favourable effect on masking the taste) and soluble in the gastric tract. However if the passage of the product is particularly rapid, as can happen with particles of small dimensions and on an empty stomach, there is a risk of having an incomplete dissolution of the membrane and so an incomplete absorption of the drug.

The present invention also differs from that described in patent EP-A-0101418 where substances, e.g. carbohydrates and polysaccharides, are added to formulations containing drugs coated with, for example, semipermeable and pH independent membranes. These substances prevent or slow down the release of the drug across the membrane, whereas in the present invention, the acidic compounds prevent the dissolution of the membrane coating on the drug rather than the dissolution of the drug.

Mapelli at 3.

In order to mask the unpleasant taste of the drug, this is coated with a membrane comprising polymers having a pH dependent solubility and more particularly polymers insoluble in an acidic environment and soluble at pH 5 or higher.

As illustrative but not limiting examples of these poloymers are cited: copolymers of methacrylic acid and methacrylic acid methyl ester (eg Eudragit L, Eudragit S), and copolymers of methacrylic acid ethyl ester (eg Eudragit L30D and L100-55), cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, shellac,

Mapelli at 4.

-5-

hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, cellulose acetate trimellitate or a copolymer of maleic acid and phthalic acid derivatives.

Mapelli at 5.

The coated drug granules are very fine and irregular and therefore have a large surface area. Consequently the membrane is only a few micrometers thick, even when the percentage weight of the membrane is high, and thus in the brief time in which all or some of the particles remain, wholly or partially in the oral cavity, a dissolution or swelling, even partial, of the membrane can occur with consequent liberation of the unpleasant taste.

It has now been found that this difficulty can be avoided or minimized according to the present invention if an acidic substance is added to the formulation in a quantity such as to maintain a microenvironment at a pH of less than 5 during the transit stage in the oropharyngeal cavity. Obviously the more acidic the microenvironment the better it is, although an excess of acid can itself give an unpleasant flavour.

Id.

It has been found that the optimum quantity of acid varies as a function of the weight of the final pharmaceutical formulation. Preferably 1% to 20% by weight of acid compound is used. As illustrative but not limiting examples of acid compounds the following are cited: fumaric acid, citric acid and tartaric acid.

Mapelli at 6.

Reuter dislcoses

(a) Field of the Invention

This invention relates to a novel therapeutic form of spray dried ibuprofen having a neutral taste which can be formulated into, for example, chewable tablets and fast dissolving dosage forms as described in U.S. Pat. Nos. 4,305,502 and 4,371,516. More specifically this invention relates to a taste-neutral spray dried powder formed by spray drying a solution of ibuprofen and ethylcellulose, hydroxyethyl cellulose or hydroxypropylmethyl cellulose alone or in admixture, in at least a 50% lower alkanol solution having suspended therein colloidal silica. By taste-neutral it is meant that the powder has essentially no taste and is neither sweet nor bitter.

Col. 1

The use of flavor agents eg. chocolate, banana, orange, lemon, licorice, root beer, and raspberry, in particular, have been proposed for bitter tasting drugs. These agents are not dependable masking ingredients. Mint flavors can be useful in ameliorating a chalky taste parameter. Bitter properties, however, are very difficult to mask to any great extent, particularly, when they do not mimic the expected natural taste of the flavor agent. Col.. 1

3

Food acids, eg. fumaric acid and malic acid, which are soluble in alkanol solutions and can create an aqueous environment not greater than pH 4.0, may correct the perception of bitterness in preparing the spray dried powder.

EXAMPLE 1

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient in suspension
Ibuprofen, USP	60.6	100
Hydroxyethyl Cellulose, NF	30.3	50
Colloidal Silica	6.06	10
Castor Oil	3.03	5
Isopropyl Alcohol, 67%	—	q.s 1000 ml.
Total:	100%	1165 grams

The ibuprofen was dissolved in a portion of the alcohol contained in a stainless steel mixing vessel with the aid of a Lightnin mixer. The hydroxyethyl cellulose was wetted and dispersed in the remaining alcohol in a separate stainless steel mixing vessel with the aid of a Lightnin mixer. The contents of the two mixing vessels were filtered and combined. The caster oil and then colloidal silica were added and mixed until a homogeneous dispersion was obtained. The dispersion was then transferred to the feed hopper of the Buchi Mini Spray Dryer.

The spray dryer was operated such that an air inlet temperature of 153°-210° C. and an air outlet temperature of 94° to 108° C. was maintained throughout the run.

The yield of spray dried powder was about 90% of theoretical. The product was a white, fine powder.

The freshly obtained product upon tasting and beng held in the mouth for 45 seconds produced no bitterness characteristic of ibuprofen. Upon aging one month at room temperature the product remained quite acceptable without bitterness.

EXAMPLE 2

This example describes the preparation of fast dissolving dosage forms using the spray dried taste-neutral ibuprofen of Example 1 and other ingredients as follows: Col. 3

Ingredient	Weight % suspension	Grams in suspension
Gelatin, BY 19/50	4.0	10.00
Mannitol, granular	3.0	7.50
Deionized water	67.10	167.75
NUTRASWEET, NF	1.20	3.00
Cherry #271	0.40	1.00
Cream Flavor #59.200/A	0.20	0.50
Sodium lauryl sulfate	0.10	0.25
Croscarmellose sodium, Type A	1.00	2.50
Powder, Example I	23.0	57.50

EXAMPLE 4

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient per 100 ml of suspension
Ibuprofen, USP	53.2	125
Isopropyl Alcohol	—	200.00
Ethyl Cellulose, NF	21.3	50
Colloidal Silica	17%	40
Castor Oil	4.25	10
Fumaric Acid	4.25	10
Isopropyl Alcohol	—	q.s. 1000 ml.
Total:	100%	

EXAMPLE 5

In this example, ethyl alcohol was used instead of isopropyl alcohol and the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Grams Ingredient per 1000 ml suspension	Weight % Solids in Powder
Ibuprofen, USP	115	54.8
Ethyl Cellulose, NF	50	23.8
Colloidal Silica	25	11.9
Hydroxypropylmethyl Cellulose	5	2.4
Castor Oil	10	4.8
Fumaric Acid	5	2.4
Ethyl Alcohol	q.s. 1000 ml.	100%

In making the rejection, the Examiner asserted that:

The claims are directed toward an oral composition comprising a racemic mixture of ibuprofen or derivative and 50-150 wt% fumaric acid (or 60%, 7-13%). The claims are also directed toward the composition of ibuprofen wherein the drug are coated particles and comprise excipients and the polymeric coating is hydrocolloid. The claims are further drawn toward the composition in tablet, chewable dosage, liquid, suckable solid or semi-solid form; the composition reduces the burn sensation of ibuprofen.

(Office Action at 5.)

As mentioned, Loew et al (Patent '227) disclose a pharmaceutical composition comprising a racemic mixture of ibuprofen (col 6, lin 10-15, lin 50-60; col 7, Table 1; lin 60-65 and col12, lin 15-30).

(*Id.*)

Patent '227 does not teach the use of fumaric acid as excipients and does not teach that ibuprofen drug particles are used for making the composition.

We discussed Mapelli et al (WO '043) above. WO '043 discloses the use of polymer-coating before granulation (page 4, lin 10), discloses the use of polymer for coating (page 4, lin 24, continuing to page 5, lin 1-5) and discloses the use of excipients such as fumaric acid (page 2, lin 25-30; page 5, lin 1-6; page 6, lin 1-5 and page 12, lin claims 2-5; and page 12, claim 2). WO '043provides a method of masking the undesirable taste of the drugs by coating with polymeric membranes (page 2, lin 25-30 and page 13, claim 10). WO '043 discloses formulations of the drug such as tablet, sachet and formulation that is easily disintegrated in the mouth (page 6, lin 10).

Reuter et al (Patent '187) is relied upon for the disclosure of powdered ibuprofen composition comprising cellulose and hydroxyethyl cellulose, sodium lauryl sulfate and fumaric acid (col 4, lin 1-10, col 5, Example 4 and Example 5). Significantly, Patent '187 discloses that the composition is taste neutral (col 3, lin 55-60 and col8, lin 10-15).

(Office Action at 6.)

The Examiner reasoned that one of ordinary skill would have been motivated to prepare pharmaceutical composition comprising racemic mixture of ibuprofen- generally known to have an unpleasant taste- and mask such unpleasant taste by coating with polymeric membranes and/or adding excipients such as malic acid, fumaric acid. (Office Action at 6.) The Examiner further reasoned that one of ordinary skill would expect to obtain organoleptically acceptable compositions of ibuprofen that would [be] more appealing and suitable to patient taste and thereby improve patient compliance in taking medication. (*Id.*) The Examiner concluded that "the invention as a whole would have been obvious to one of ordinary skill in the art at the time it was made." (*Id.*)

The Examiner commented on an updated search that "further strengthen[ed] the examiner's position for maintaining the rejection of record." (Paper No. 20051108 at 2.) The Examiner did not, however, make any new document of record in the instant case. It is, therefore, not possible to evaluate the factual record relied on by the Examiner to make the above statement. Therefore, it is requested that the Examiner provide clarification of the Examiner's position in the next paper issued in the captioned application.

As is fundamental, a *prima facie* case of obviousness must be based on facts, "cold hard facts." When the rejection is not supported by facts, it cannot stand. The rejection uses facts related to compositions to reject method claims. It is not seen in this record where there are any facts to support such reasoning. Thus, the rejection is not supported by facts and must be withdrawn for this reason alone.

Even if the rejection were proper, which is denied, it ignores the fact that it appears that Loew teaches away from the claimed invention. In particular, Loew discloses advantages of using the (S)-(+)-ibuprofen over the racemic mixture or its racemate. It is not seen where one of ordinary skill in the art would be motivated to use racemic ibuprofen in the method of the claimed invention. Nor is it seen where Mapelli and Reuter provide the necessary motivation.

A *prima facie* case of obviousness, however, requires that the rejection describe with specificity **why** one skilled in the art would have combined two references to arrive at the claimed invention. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (CAFC 1999). ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of *the requirement for a showing of the teaching or motivation to combine prior art references*."). In the present case, no such explanation is found in the rejection. The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

The Examiner responded to the above, with the following:

In response, the instant claims are method claims drawn toward reducing the burning sensation of propionic acid derivative (ibuprofen). In giving the broadest interpretation for the claims, examiner takes the position that the method claims are inexorably linked to the composition claims because the final product, i.e. the ibuprofen formulation, has to taken by a patient in order to realize the benefits, if any of the drug; --namely the reduction in the burning sensations (unpleasant taste).

(Office Action at 7.)

With this as the background, the Sec 103(a) obviousness rejection is maintained given the disclosures in prior art cited as explained supra. Respecting this issue, Mapelli specifically discloses a process or method for masking the taste of ibuprofen to reduce or prevent dissolution of the drug in the oral cavity by coating the granulate core during preparation of tablets (Patent '711, col 2, lin 24-45; col 3, lin 1-5, col 4, lin 21-25, lin 51-60; col 5, lin 1-10 and col 6, lin 40-46). Furthermore, Reuter et al discloses improvement in ibuprofen dosage form when the drug is

(Id.)

spray-dried with taste-neutral cellulose materials or admixtures thereof (Patent '187, col 6, lin 60-68, continuing to cols 7-8. Finally, the disclosures in both Mapelli and Reuter are reinforced by the relevant inferential disclosure in Humber—that taste masking of ibuprofen may be achieved by coating the drug with suitable materials, preferably material that cannot be easily punctured by chewing (Patent '046, col 2, lin 44-63). Therefore, the instant claims drawn to a method of reducing burning sensations of proprionic aci derivative i.e. ibuprofen by coating the drug with fumaric fumaric acid and other excipients would have been prima facie obvious to one of ordinary skill at the time it was made given that the prior art cited have used the excipients for the purpose of eliminating or preventing unpleasant taste of ibuprofen.

(Office Action at 8)

It is still not seen where the Examiner has presented any facts to support using the claimed racemic mixture in view of Lowe's disclosure favoring the (S)-(+) ibuprofen. In fact, the Examiner's reasoning in response to the Applicant's position did not specifically

address where such motivation was to be found. The factual record does not support the rejection. For this reason, the rejection is improper and should be withdrawn.

Even further, the Examiner cites to "Patent '711" presumably in a discussion of Mapelli. Unfortunately, it is not seen where a "Patent '711" was relied on by the Examiner to make the instant rejection. The Examiner is asked to clarify the factual basis to support the use of Mapelli to make the instant argument.

The Examiner also relied on an uncited document in setting for reasoning that the instant rejection is proper. (Office Action at 8.) In particular, the Exmainer relied on "relevant inferential disclosure in Humber" to support the Examiner's position. With all due respect Humber was not used to reject claims 15-22. Any reliance on Humber is therefore, improper and must be withdrawn.

Accordingly, entry of the claims and allowance of the claims is respectfully requested.

Finally, the Examiner is invited to call the applicants' undersigned representative if any further action will expedite the prosecution of the application or if the Examiner has any suggestions or questions concerning the application or the present Response. In fact, if the claims of the application are not believed to be in full condition for allowance, for any reason, the applicants respectfully request the constructive assistance and suggestions of the Examiner in drafting one or more acceptable claims pursuant to MPEP § 707.07(j) or in making constructive suggestions pursuant to MPEP § 706.03 so that the application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,

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Dated: December 14, 2005